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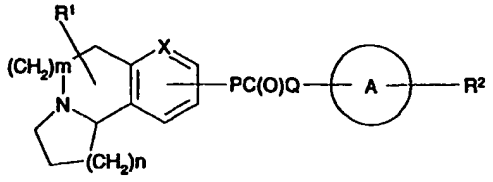

(I)

(57) Abstract

Compounds of formula (I) or salts thereof or solvates thereof in which: X is CH or N; P is –CH=CH– and Q is –NR^6–, or; P is –CH=CH– and Q is –NR^6CH2–, or; P is –NH– and Q is –CR^3=CH–; R^6 is hydrogen, phenylC_{1-6}alkyl, or C_{1-6}alkyl; R^3 is hydrogen, halo, phenylC_{1-6}alkyl, or C_{1-6}alkyl; A is a monocyclic aromatic carbocyclic or heterocyclic compound or a bicyclic carbocyclic or heterocyclic compound in which one ring is aromatic; m is 1 or 2; n is 1 or 2; R^1 is hydrogen or up to two substituents selected from fluoro or C_{1-6}alkyl; R^2 is hydrogen or up to four substituents selected from halogen, NO_2, CN, N_3, CF_3O–, CF_3S–, CF_3CO–, trifluoromethyldiazirinyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl–C_{1-4}alkyl–, C_{1-6}alkyl$O$–, C_{1-6}alkylCO–, C_{3-6}cycloalkyl$O$–, C_{3-6}cycloalkylCO–, C_{3-6}cycloalkyl–C_{1-4}alkyl$O$–, C_{3-6}cycloalkyl–C_{1-4}alkylCO–, phenyl, phenoxy, benzyloxy, benzoyl, phenyl–C_{1-4}alkyl–, C_{1-6}alkyl$S$–, C_{1-6}alkylSO_2–, $(C_{1-4}alkyl)_2NSO_2$–, $(C_{1-4}alkyl)NHSO_2$–, $(C_{1-4}alkyl)_2NCO$–, oxazolyl, $(C_{1-4}alkyl)NHCO$– or $CONH_2$; or –NR^4R^5 or –NHCOR [4] where R^4 is hydrogen or C_{1-4}alkyl, and; R^5 is hydrogen, C_{1-4}alkyl, formyl, –CO_2C_{1-4}alkyl or –COC_{1-4}alkyl; or two R^2 groups are linked together to form a carbocyclic or heterocyclic ring that is saturated or unsaturated and unsubsituted or substituted by –OH or =O; R^3 is hydrogen, halogen, phenylC_{1-6}alkyl, or C_{1-6}alkyl; or R^3 and R_2 are linked together form a saturated or unsaturated carbocyclic or heterocyclic ring are indicated to be useful in the treatment and prophylaxis of epilepsy, migraine, and other disorders.

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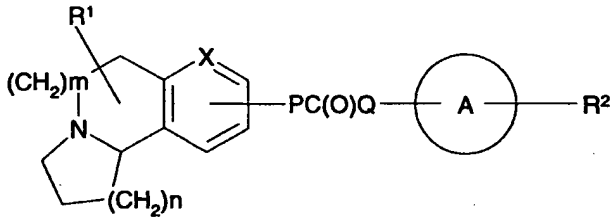
CONDENSED TRICYCLIC PIPERIDINES HAVING ANTI-CONVULSANT ACTIVITY

This invention relates to novel compounds, to processes for preparing them, and to their use as therapeutic agents.

It has now been surprisingly found that tricyclic/carboxamide compounds of formula (I) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

Accordingly, the present invention provides a compound of formula (I) or a salt thereof or a solvate thereof



(I)

in which:

X is CH or N;

P is -CH=CH- and Q is -NR^6-, or;

P is -CH=CH- and Q is –NR^6CH2-, or;

P is –NH- and Q is –CR^3=CH-;

R^6 is hydrogen, phenylC_{1-6}alkyl, or C_{1-6}alkyl;

R^3 is hydrogen, halo, phenylC_{1-6}alkyl, or C_{1-6}alkyl;

A is a monocyclic aromatic carbocyclic or heterocyclic compound or a bicyclic carbocyclic or heterocyclic compound in which one ring is aromatic;

m is 1 or 2;

n is 1 or 2;

R^1, which may be at any position within the saturated ring system, is hydrogen or up to two substituents selected from fluoro or C_{1-6} alkyl;

R^2 is hydrogen or up to four substituents selected from halogen, NO_2, CN, N_3, CF_3O-, CF_3S-, CF_3CO-, trifluoromethyldiazirinyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkylO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, C_{1-6}alkylS-, C_{1-6}alkylSO_2-, $(C_{1-4}alkyl)_2NSO_2$-, $(C_{1-4}alkyl)NHSO_2$-, $(C_{1-4}alkyl)_2NCO$- , oxazolyl, $(C_{1-4}alkyl)NHCO$- or $CONH_2$;

or -NR^4R^5 or -$NHCOR^4$ where R^4 is hydrogen or C_{1-4} alkyl, and;

R^5 is hydrogen, C_{1-4}alkyl, formyl, -CO_2C_{1-4}alkyl or -COC_{1-4}alkyl;

or two R^2 groups are linked together to form a carbocyclic or heterocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O;

R^3 is hydrogen, halogen, phenylC_{1-6} alkyl, or C_{1-6} alkyl;

or R^3 and an R^2 are linked together to form a saturated or unsaturated carbocyclic or heterocyclic ring.

When ring A is heterocyclic, A may be for example furanyl, thiophenyl, indolinyl or indazolinyl. The ring A is typically optionally substituted phenyl or optionally substituted thiophenyl, preferably substituted phenyl.

When two R^2 groups are linked to form a ring, this is typically a 5-6 membered ring, so that when A is phenyl the resultant bicyclic [A - R^2 /R^2] fused ring may be a naphthalene or an indane or indanone or indolyl ring system.

In the formula (I), alkyl groups, including alkyl groups that are part of another moiety, may be straight chain or branched. Aromatic rings, especially phenyl groups, including rings that are part of another moiety, may optionally be substituted with one or more independently selected halogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylcarbonyl groups. Suitable halo substituents include fluoro, chloro, iodo and bromo. Suitable C_{3-6} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups.

When used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Preferably a substituent for a heterocyclyl group is selected from halogen, (C_{1-6})alkyl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-N-(C_{1-6})alkyl-amino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbonyl, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryloxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl(C_{1-6})alkyl.

It should be appreciated that the compounds of formula (I) have one or more chiral carbon atoms and therefore may exist as enantiomers . The present invention extends to each enantiomer and to mixtures thereof including racemates and diastereomers.

A suitable group of compounds of formula (I) have

R^1 as hydrogen, fluoro, methyl, ethyl or propyl;

R^2 as hydrogen or one or more of methyl, ethyl, *n*-butyl, phenyl, *iso*-propyl, *t*-butyl, methoxy, ethoxy, n-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amino, acetylamino, methylthio, oxazolo, methylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl;

R^3 as hydrogen, fluoro, methyl, ethyl or propyl.

Suitable linked R^2 groups include -CH=CH-NH-.

In a particular group of compounds of formula (I),

R^1 is hydrogen,

R^2 is hydrogen or one or more of ethyl, methoxy, trifluoromethyl, cyano, chloro, fluoro.

Examples of compounds of formula (I) are:

3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;

3-(2-Methoxyphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;

3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Chlorophenyl)-N-(6,6-dimethyl-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Chloro-6-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Acetylaminophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Acetylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Cyanophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)-3-[2-(2-oxopyrrolidin-1-yl)phenyl]acrylamide;
3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Methylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Nitrophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Trifluoromethylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(3-Trifluoromethylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(4-Chloro-2-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Chloro-6-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide, and;
3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)-N-(3-methylphenyl)acrylamide.

When synthesised, these compounds may be isolated in salt form, such as the hydrochloride or trifluoroacetate, and such salts also form part of this invention. Such salts may be used in preparing pharmaceutically acceptable salts. The compounds and their salts may be obtained as solvates, such as hydrates, and these also form part of this invention.

The above compounds and pharmaceutically acceptable salts thereof, especially the hydrochloride, and pharmaceutically acceptable solvates, especially hydrates, form a preferred aspect of the present invention.

The administration of such compounds to a mammal may be by way of oral, parenteral, sub-lingual, nasal, rectal or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that the compound of formula (I) is administered in the form of a unit-dose composition, such as a unit dose oral, including sub-lingual, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colorants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art. Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin,

hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents. Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

Accordingly, the present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral

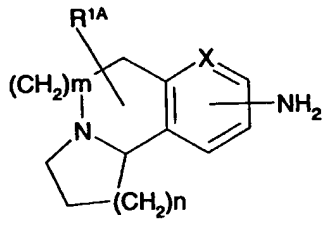
sclerosis (ALS), which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides a method of treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

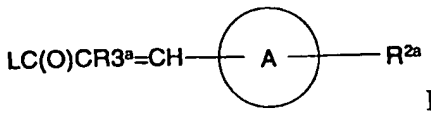
In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

The present invention also provides a process for the preparation of compounds of formula (I) or a salt thereof or a solvate thereof wherein P is –NH- and Q is $-CR^3=CH-$, which comprises reacting a compound of formula (II)



(II)

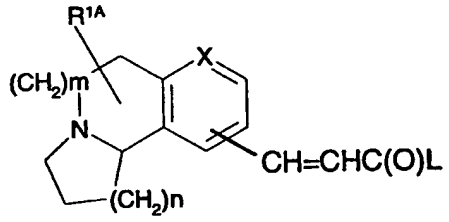
where m and n are as defined for formula (I), R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1;
with a compound of formula (III)



III)

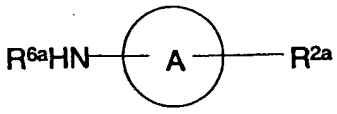
where R^{2a} and R^{3a} are independently R^2 or R^3 as defined for formula (I) or a group or groups convertible to R^2 or R^3; A is as defined for formula (I), and L is OH, acyloxy, or a halogen;
and where required,
converting an R^{1A}, R^{2a} or R^{3a} group to an R^1, R^2 or R^3 group;
converting one R^1, R^2 or R^3 group to another R^1, R^2 or R^3 group;
converting a salt product to the free base or another pharmaceutically acceptable salt, or;
converting a free base product to a pharmaceutically acceptable salt.

The present invention also provides a process for the preparation of compounds of formula (I) or a salt thereof or a solvate thereof wherein P is –CH=CH- and Q is —NR^6-, or where P is –CH=CH- and Q is —CH_2NR^6-which comprises reacting a compound of formula (IV)

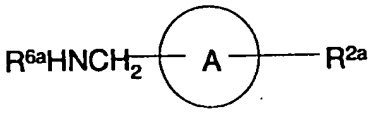


(IV)

where m and n are as defined for formula (I), R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1;
with a compound of formula (V) or (VI)



(V)



(VI)

where R^{2a} and R^{6a} are independently R^2 or R^6 as defined for formula (I) or a group or groups convertible to R^2 or R^6; A is as defined for formula (I), and L is OH, acyloxy, or a halogen;
and where required,
converting an R^{1A}, R^{2a} or R^{6a} group to an R^1, R^2 or R^6 group;

converting one R^1, R^2 or R^6 group to another R^1, R^2 or R^6 group;
converting a salt product to the free base or another pharmaceutically acceptable salt, or;
converting a free base product to a pharmaceutically acceptable salt.

Conventional conditions for condensation of amines with carboxylic acids or active derivatives thereof, such as acid chlorides, may be used. For example the amines and acids may be reacted in the presence of a mixture of ethyl(dimethylaminopropyl)-carbodiimide/hydroxybenzotriazole in a suitable solvent such as dimethyl formamide. Amines and acid chlorides may be reacted together in a suitable solvent such as ethyl acetate or tetrahydrofuran, in the presence of a base such as triethylamine. Alternatively the acid may be treated in solution with oxalyl chloride and then reacted with the amine or its hydrochloride.

Reaction of a compound of formula (III) which is an acid chloride (L=Cl) with a compound of formula (II) will, in the absence of a base such as triethylamine, result in formation of the hydrochloride salt of the compound of formula (I). Similarly reaction of a compound of formula (IV) with a compound of formula (V) or (VI) will, in the absence of a base such as triethylamine, result in formation of the hydrochloride salt of the compound of formula (I). Hydrochloride salts can be obtained by also be obtained by passing HCl gas into a solution of the free base, or adding a solution of HCl in ether.

Conversions of an R^{1A}, R^{2A}, R^{3a} or R^{6a} group to an R^1, R^2, R^3 or R^6 group typically arise when a protecting group is needed during the above coupling reaction or during the preparation of the reactants by the procedures described below. Interconversion of one R^1, R^2,R^3 or R^6 group to another typically arises when one compound of formula (I) is used as the precursor of another compound of formula (I) or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

The compounds of formula (II) and (IV) have chiral carbon atoms and therefore may exist as enantiomers. Accordingly the above process may produce compounds of formula (I) that are racemic mixtures. These mixtures may be separated or resolved by conventional procedures if individual enantiomers are required. Alternatively the starting materials may be selected to achieve a stereospecific reaction.

Compounds of formula (II) may be prepared from the corresponding hexahydro-pyrido/pyrollo-isoquinolines, firstly forming a nitro compound and then hydrogenating the nitro group to the amine. The nitro group may be introduced by treating the hexahydro-pyrido/pyrollo-isoquinoline with concentrated sulfuric acid and adding potassium nitrate. Hydrogenation of the

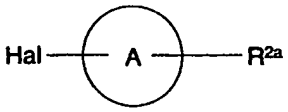
nitro compound may be carried out by reaction with hydrogen at 50 psi in the presence of palladium/charcoal in a suitable solvent such as ethanol.

Compounds of formula (IV) maybe prepared from the corresponding aminohexahydro-pyrido/pyrollo-isoquinolines by converting the amine to a halogen such as bromo for example by diazotisation with sodium nitrite and treatment of the resulting diazo salt with copper (I) bromide and subsequent treatment with ethyl acrylate in the presence of a palladium catalyst under conventional conditions.. For example the reactants may be heated in the presence of palladium acetate and triethylamine in a suitable solvent such as acetonitrile. This reaction produces the corresponding ester of the L = OH compound of formula (III). Deesterification, for example by treatment with sodium or potassium hydroxide, gives the acid (L = OH) of formula (III).

The hexahydro-pyrido-isoquinoline starting materials may be prepared by analogous methods to those described in J. Pharm Bull, 1960, 8, 14.

Hexahydro-pyrrolo-isoquinolinylamines may be prepared by analogy to the methods disclosed in WO 97/17344 (Astra Aktibolag).

Compounds of Formula (III) in which R^{3a} is hydrogen or a halo, alkyl or phenylalkyl substituent may be prepared by initially reacting a compound of formula (IV)



(VII)

where Hal is a halogen, with an acrylate ester under conventional conditions. For example the reactants may be heated in the presence of palladium acetate and triethylamine in a suitable solvent such as acetonitrile. This reaction produces the corresponding ester of the L = OH compound of formula (III). Deesterification, for example by treatment with sodium or potassium hydroxide, gives the acid (L = OH) of formula (III). The acid of formula (III) can be reacted with the amine of formula (II) under conditions mentioned above for reaction of formulae (II) and (III), or converted to the acid chloride, for example by treatment with carbonyl chloride, and then reacted with the amine.

The halo compounds of formula (VII) are commercially available or can be prepared by standard methods.

When A is phenyl, compounds of formula (III) are cinnamic acid derivatives.

Where the above described intermediates are novel compounds, they also form part of this invention.

The preparation of compounds of formulae (II) and (IV) is illustrated by the following **Descriptions**; the preparation of compounds of this invention is illustrated by the following **Examples**. The utility of compounds of this invention is shown by the **Pharmacological Data** that follow the Examples.

Description 1
(+/-)-7-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline and (+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline
From the nitration of 1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (3.5g) according to the method of WO 97/17344 (+/-)-7-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (0.35g) and (+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (3.6g) were isolated by column chromatography (silica gel, 10% methanol:diethyl ether).
Description D1a: Characterisation of (+/-)-7-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline
^{1}H NMR (400MHz, $CDCl_3$) δ:1.70 - 1.81 (1H, m), 1.86 - 2.05 (2H, m), 2.37 - 2.43 (1H, m), 2.52 - 2.64 (2H, m), 3.07 - 3.47 (5H, m), 7.24 - 7.35 (2H, m) and 7.77 (1H, d, 7.16Hz).
Description D1b: Characterisation of (+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline
^{1}H NMR (250MHz, $CDCl_3$) δ:1.72 – 2.01 (3H, m), 2.47 – 2.70 (3H, m), 2.90 – 3.10 (1H, m), 3.10 – 3.32 (3H, m), 3.39 (1H, t), 7.27 (1H, d, J = 8.3Hz), 7.95 (1H, s) and 7.99 (1H, dd, J = 2.3, 8.3Hz)
MS $^m/_z$ (API): 219 (MH^+; 100%).

Description 2
(+/-)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-7-ylamine
A solution of nitro compound D1a (0.30g) in ethanol (20ml) and palladium on charcoal (5% w/w, 0.1g) was hydrogenated at 50psi at room temperature for 2h. The reaction mixture was filtered through a celite pad and the filtrate evaporated to dryness to give the title compound (0.22g) as an oil.
^{1}H NMR (250MHz, $CDCl_3$) δ: 1.67 - 2.00 (3H, m), 2.27 - 2.82 (5H, m), 3.12 (1H, dt, J = 2.62 and 7.99Hz), 3.25 - 3.34 (2H, m), 6.54 (2H, d, J = 7.75Hz) and 6.98 (1H, t, J = 7.69).
MS $^m/_z$ (API): 189 (MH^+; 100%)

Description 3
(+/-)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-ylamine

From nitro compound D1b (4.0g) the title compound (3.5g) was prepared according to the method of Description 2.
^{1}H NMR (250MHz, $CDCl_3$) 1.63 – 2.03 (3H, m), 2.23 – 2.38 (1H, m), 2.49 – 2.78 (3H, m), 2.93 – 3.24 (3H, m), 3.39 (1H, t), 6.42 (1H, d, J = 2.3Hz), 6.50 (1H, dd, J = 2.4, 7.9Hz) and 6.90 (1H, d, J = 7.9Hz).
MS $^m/_z$ (API): 189 (MH^+; 100%).

Description 4
(+)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline and (-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline.
(+/-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D1b) (50g) was separated into the two enantiomers by simulated moving bed chromatography using eight columns packed with 30g of Chiralpak AD and 10% ethanol in hexane (containing 0.1% diethylamine) as the eluant with the following system parameters: recycle flow rate = 101.64ml/min, feed = 1.04ml/min, eluent = 20.21ml/min, raffinate = 5.78ml/min, extract = 15.48ml/min, feed concentration = 9g/l, switch period = 1.18min. 19g of each enantiomer (e.e. > 95%) was obtained.
First eluting component (+)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4a)
Second eluting component (-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4b)

Description 5
(-)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-ylamine
From (-)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4b) (0.5g) the title compound (0.454g) was prepared according to the method of Description 2 using 5%pd/C (0.2g) and hydrogenating for 45min at room temperature..
Spectral data identical to the compound of Description 3.
$[\alpha]_D^{25}$ -111° (c 1.0, MeOH).

Description 6
(+)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-ylamine
From (+)-9-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (D4a) (0.25g) the title compound (0.183g) was prepared according to the method of Description 2 using 5%pd/C (0.15g) and hydrogenating for 45min at room temperature..
Spectral data identical to the compound of Description 3.
$[\alpha]_D^{25}$ +123° (c 0.5, MeOH).

Description 7

Dimethylphenylacetonitrile

Phenylacetonitrile (11.7g) was dissolved in dimethyl sulphoxide/water (96ml 80:16). Sodium hydroxide (16.0g) was added to the rapidly stirred mixture. Iodomethane (25ml) was added over 30 min (exotherm). The mixture was stirred for 1h, partitioned between diethyl ether:water and the ether layer separated. The ether layer was washed with water and brine, dried ($MgSO_4$) and solvent removed at reduced pressure to give the title compound (13.8g).

^1H NMR (250MHz, $CDCl_3$) δ 1.73 (6H, s), 7.29 – 7.50 (5H, m).

Description 8

4-Chloro-N-2-methyl-2-phenylpropane

Lithium aluminium hydride (5.42g) was stirred in diethyl ether (250ml). Dimethylphenylacetonitrile (13.8g) in diethyl ether (50ml) was added over 30 min at room temperature. When the addition was complete the reaction mixture was warmed to reflux for 3h, cooled (ice bath) and wet tetrahydrofuran CAREFULLY added. The mixture was subsequently quenched with water and 2N sodium hydroxide(11ml). The suspension was stirred for 30min, filtered, the organic phase isolated and dried (MgSO4). Solvent was removed at reduced pressure to give the title compound (13.8g) as an oil.

MS m/z (API): 150 (MH+; 100%)

Description 9

4-Chloro-N-(2-methyl-2-phenylpropyl)butyramide

4-Chloro-N-2-methyl-2-phenylpropane (D8) in tetrahydrofuran (250ml) containing triethylamine (12.88ml) was treated with 4-chlorobutyryl chloride (10.37ml) with stirring. After stirring overnight, the reaction mixture was partitioned between diethyl ether/water, the organic phase separated washed with water, dried ($MgSO_4$) and solvent removed at reduced pressure to give the title compound (23.08g) as an oil.

MS m/z (API): 254, 256 (MH^+; 100%)

Description 10

6,6-Dimethyl-2,3,5,6-tetrahydro-1H-pyrrolo[2,1-a]isoquinolinylium nitrate

The amide D9 (10.0g) in xylene (200ml) was treated with phosphorous pentoxide (25g) and phosphorous oxychloride (25g) subsequently added carefully. The mixture was boiled for 7h. cooled and the solvent decanted. The residue was dissolved in water, acidified with conc. HCl and the aqueous phase washed with toluene. The aqueous phase was basified with excess potassium carbonate, washed with toluene and treated with potassium iodide (20g). The aqueous

mixture was extracted with dichloromethane (x2), the combined organic phase dried (MgSO4) and solvent removed at reduced pressure to give after trituration with acetone the title compound as a brown solid (8.47g).
The iodide salt was converted to the nitrate salt by dissolving the iodide (9.4g) in acetonitrile (250ml). Silver nitrate (4.89g) in acetonitrile (100ml) was added dropwise over 30 min. The mixture was stirred for a further 30 min, filtered and solvent removed at reduced pressure to give after trituration with acetone the title compound (6.48g) as a colourless solid.
^{1}H NMR (250MHz, $CDCl_3$) δ 1.40 (6H, s), 2.52 (2H, m), 3.69 – 3.77 (2H, m), 3.94 (2H, s), 4.52 (2H, m), 7.45 – 7.53 (2H, m) and 7.74 – 7.80 (2H, m).

Description 11
6,6-Dimethyl-2,3,5,6-tetrahydro-1H-pyrrolo[2,1-a]-9-nitro-isoquinolinylium iodide
The nitrate salt D10 (6.48g) was added as a solid in portions over 1h to conc. sulphuric acid pre-cooled to –10 - -15°C **internal** temperature. After addition was complete the mixture was warmed to 0°C (internal temperature) and stirred for 1h. The reaction mixture was adjusted to pH10 by addition to sat. potassium hydroxide, pH adjusted to 3 with conc. HCl excess potassium iodide added and extracted with dichloromethane (10 x 100ml). The combined organic phase was dried (MgSO4) and solvent removed at reduced pressure to give the title compound (7.83g) after trituration with acetone.
^{1}H NMR (250MHz, $CDCl_3$) δ 1.50 (6H, s), 2.65 (2H, m), 3.98 – 4.05 (2H, m), 4.11 (2H, s), 4.50 – 4.57 (2H, m), 7.74 (1H, d, J = 7.6Hz) and 8.57 – 8.61 (2H, m).

Description 12
(+/-)-6,6-Dimethyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]-9-nitro-isoquinoline
The compound D11 (7.0g) was suspended in methanol and sodium borohydride (1.43g) added over 1h. The mixture was stirred for a further 1h after addition was complete, saturated potassium carbonate added and solvent removed at reduced pressure. The residue was extracted with dichloromethane (3 x 100ml), the organic phases were combined, dried ($MgSO_4$) and solvent removed at reduced pressure to give the title compound (5.17g) as a colourless solid.
^{1}H NMR (250MHz, $CDCl_3$) δ 1.32 (3H, s), 1.39 (3H, s), 1.64 – 2.00 (3H, m), 2.34 – 2.49 (3H, m), 2.88 (1H, d, J = 11Hz), 3.08 – 3.24 (2H, m), 7.44 (1H, d, J = 8.7Hz), 7.90 (1H, d, J = 2.4Hz) and 8.03 (1H, dd, J = 2.4, 8.7Hz).

Description 13

(+/-)-6,6-Dimethy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-ylamine

The title compound (4.31g) was prepared from D12 (5.0g) according to the procedure of D2.

^{1}H NMR (250MHz, $CDCl_3$) δ 1.24 (3H, s), 1.30 (3H, s), 1.63 – 1.95 (4H, m), 2.18 – 2.30 (2H, m), 2.38 (q, J = 8.7Hz), 2.80 (1H, d, J = 10.9Hz), 3.02 – 3.18 (2H, m), 3.53 (2H, br. s.)6.39 (1H, d, J = 2.3Hz), 6.55 (1H, dd, J = 2.5, 8.3Hz) and 7.08 (1H, d, J = 8.3Hz).

MS m/z (API): 217 (MH^+; 100%)

Description 14

4-Chloro-N-phenethylbutyramide

The title compound compound (250g) was prepared from phenethylamine hydrochloride (200g) and 4-chlorobutyryl chloride (180g) according to the method of Description 9.

MS m/z (API): 226, 228 (MH^+; 100%)

Description 15

2,3,5,6-Tetrahydro-1H-pyrrolo[2,1-a]isoquinolinylium iodide

The title compound (80g) was prepared from D14 according to the method of description 10

MS m/z (API): 172 (MH^+; 100%)

Description 16

2,3,5,6-Tetrahydro-1H-pyrrolo[2,1-a]isoquinolinylium nitrate

The title compound (2.4g) was prepared from D15 (3.0g) according to the method of description 10

MS m/z (API): 172 (MH^+; 100%)

Description 17

9-Nitro-2,3,5,6-tetrahydro-1H-pyrrolo[2,1-a]isoquinolinylium iodide

The title compound (2.2g) was prepared from D16 according to the method of description 11.

^{1}H NMR (250MHz, d^6-DMSO) δ 2.33 (2H, m), 3.42 (2H, t), 3.69 (2H, m), 4.09 (2H, m), 4.31 (2H, m), 7.84 (1H, d), 8.57 – 8.65 (2H, m).

Description 18

9-Amino-2,3,5,6-tetrahydro-1H-pyrrolo[2,1-a]isoquinolinylium iodide

The nitro compound D17 (3.0g) in ethanol (200ml) containing palladium/charcoal (5% 2.0g wet weight) was shaken at 50°C under hydrogen for 16h. Catalyst was removed by filtration, solvent removed at reduced pressure and the residue hydrogenated at 50psi and 50°C in methanol:dichloromethane (200ml, 95:5) with palladium/charcoal (5% 1.5g wet weight) for 24h. After filtration solvent was removed and the residue triturated with ethanol/ether to give the title compound (2.1g).

Description 19

9-Bromo-2,3,5,6-tetrahydro-1H-pyrrolo[2,1-a]isoquinolinylium iodide

The amine D18 (3.5g) was dissolved in 48% HBr (20ml) and cooled to 0 - 4°C. Sodium nitrite (0.77g in water 2ml) was added dropwise and when the addition was complete the mixtuire was stirred for a further 10min at 0°C. Copper(I) bromide (2.15g in 48% HBr 5ml) was added and the mixture warmed to room temperature and stirred for 1h.. Potassium bromide (10g) was added and the mixture extracted with dichloromethane. Organic extracts were combined and solvent removed at reduced pressure to give the title compound (4.2g)

MS m/z (API): 250, 252 (MH^+; 100%)

Description 20

9-Bromo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline

The title compound 1.75g) was prepared from the salt D19 (4.2g) according to the method of description 12.

MS m/z (API): 252, 254 (MH^+; 100%)

Description 21

3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)acrylic acid ethyl ester

A mixture of bromo compound D20, ethyl acrylate (0.5g), palladium (II) acetate (0.08g), tri-o-tolylphosphine (0.15g) and triethylamine in acetonitrile (5ml) was boiled for 20h. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, diethyl ether/methanol 10:1) to give the title compound (0.70g)

MS m/z (API): 272 (MH^+; 100%)

Description 22

3-(1,2,3,5,6,10b-Hexahydropyrrolo[2,1-a]isoquinolin-9-yl)acrylic acid ethyl ester

A mixture of compound D21 (1.5g) in methanol:2N NaOH (30 ml 2:1) was stirred at room temperature for 1h, solvent removed at reduced pressure and the residue dissolved in water (10ml). The solution was extracted with dichloromethane, the extracts combined and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane/methanol 99:1 → 90:10) to give the title compound (0.12g)
MS m/z (API): 244 (MH^+; 100%)

Example 1

(+/-) 3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

A solution of (+/-)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-amine (0.188g), D3, 2-chlorocinnamic acid (0.18g) and N-hydroxybenzotriazole (0.05g) in dimethylformamide was treated with ethyldimethylaminopropyl carbodiimide HCl salt (0.19g) and stirred for 16h. The mixture was diluted with ethyl acetate, washed with water (x 5) dried (MgSO4) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 95% dichloromethane/methanol) to give the title compound as a free base (0.34g)
^1H NMR (250MHz, $CDCl_3$) δ: 1.67 - 1.77 (1H, m), 1.81 - 1.99 (2H, m), 2.27 - 2.35 (1H, m),2.55 - 2.68 (2H, m), 2.81 (1H, d)3.00 - 3.22 (3H, m), 3.42 (1H, t), 6.59 (1H, d, J = 15.56Hz), 7.03 (1H, d, J = 8.2Hz), 7.15 - 7.25 (2H, m), 7.30 (1H, d), 7.38, (1H, dd, J = 1.24 and 7.84Hz), 7.40 (1H, s), 7.53 (1H, d), 8.02 (1H, br. s.) and 8.10 (1H, d, J = 15.56Hz)
MS $^m/_z$ (API): 353, 355 (MH^+)

The hydrochloride salt (0.07g) was prepared from the free base (0.14g) in methanol (5ml) by addition of ethereal HCl (1M, 2ml). Solvent was removed at reduced pressure and the residue triturated with diethyl ether to give the title hydrochloride salt.
^1H NMR - resonances broadened (250MHz, $CDCl_3$) δ: 1.94 - 2.08 (3H, m), 2.50 - 2.65 (1H, m), 2.75 - 2.95 (1H, m), 3.00 - 3.33 (3H, m)3.41 (1H, m), 3.75 (1H, m), 4.40(1H, m) 6.93 (1H, d, J = 7.83Hz), 7.11 - 7.30 (3H, m), 7.38 (1H, d), 7.57 (1H, d), 7.74 (1H, d), 8.12 (1H, d) and 9.90 (1H, br. s.).

Example 2

(+/-) 3-(2-Methoxyphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.086g) was prepared from 1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-amine (0.10g) and 2-methoxycinnamic acid (0.09g) according to the method of Example 1

^{1}H NMR - resonances broadened (250MHz, d^6-DMSO) 1.86 - 2.10 (3H, m), 2.57 (1H, m), 2.89 - 3.10 (2H, m), 3.27 - 3.62 (6H, m), 3.89 (3H, s), 4.73 (1H, m), 6.92 (1H, d), 6.99 - 7.09 (2H, m), 7.23 (1H, m), 7.41 (1H, t), 7.56 (2H, m), 7.68 (1H, s) and 7.80 (1H, d).

MS $^m/_z$ (API): 349 (MH^+)

Example 3

(+) 3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.21g) was prepared from (+)1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-amine (0.17g) D6 and 2-chlorocinnamic acid (0.20g) according to the method of Example 1

^{1}H NMR - (250MHz, CDCl3 free base) 1.67 – 1.97 (3H, m), 2.37 (1H, m), 2.47 – 2.67 (2H, m), 2.76 – 2.83 (1H, m), 3.01 – 3.23 (3H, m), 3.40 (1H, m_, 6.55 (1H, d, J = 15.5Hz), 7.09 (1H, d, J = 8.2Hz), 7.29 (3H, m), 7.41` - 7.47 (3H, m), 7.58 (1H, m) and 8.12 (1H, d, J = 15Hz).

MS $^m/_z$ (API): 353, 355 (MH^+)

Chiral purity 98% (OJ column, 50/50/0.1 hexane, ethanol, trifluoroacetic acid.

Example 4

(+/-) 3-(2-Chlorophenyl)-N-(6,6-dimethyl-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.281g) was prepared from amine D13 and 2-chlorocinnamic acid (0.18g) according to the method of Example 1

^{1}H NMR - (250MHz, CDCl3 free base) 1.28 (3H, s), 1.34 (3H, s), 1.71 – 2.05 (3H, m), 2.31 (2H, m), 2.43 (1H, q), 2.84 (1H, d, J = 11Hz), 3.05 (1H, m), 3.19 (1H, m), 6.56 (1H, d, J = 15.5Hz), 7.23 – 7.33 (3H, m), 7.40 – 7.46 (3H, m), 7.58 (1H, m) and 8.13 (1H, d, J = 15.5Hz).

MS $^m/_z$ (API): 383, 385 (MH^+)

Example 5

(+) 3-(2-Chloro-6-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.30g) was prepared from amine D6 (0.18g) and 2-chloro-6-fluorocinnamic acid (0.18g) according to the method of Example 1

MS $^m/_z$ (API): 371, 373 (MH^+)

Example 6

(+) 3-(2-Acetylaminophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.265g) was prepared from amine D6 (0.18g) and 2-acetylaminocinnamic acid (0.185g) according to the method of Example 1

MS $^{m}/_{z}$ (API): 376 (MH^+)

Example 7

(+) 3-(2-Acetylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.305g) was prepared from amine D6 (0.18g) and 2-acetylcinnamic acid (0.171g) according to the method of Example 1

MS $^{m}/_{z}$ (API): 361 (MH^+)

Example 8

(+) 3-(2-Cyanophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.205g) was prepared from amine D6 (0.18g) and 2-cyanocinnamic acid (0.156g) according to the method of Example 1

MS $^{m}/_{z}$ (API): 344 (MH^+)

Example 9

(+) N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)-3-[2-(2-oxopyrrolidin-1-yl)phenyl]acrylamide hydrochloride

The title compound (0.255g) was prepared from amine D6 (0.18g) and 2-cyanocinnamic acid (0.172g) according to the method of Example 1

MS $^{m}/_{z}$ (API): 401 (MH^+)

Example 10

(-) 3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.31g) was prepared from amine D5 (0.188g) and 2-chlorocinnamic acid (0.18g) according to the method of Example 1

MS $^{m}/_{z}$ (API): 353, 355 (MH^+)

Example 11

(+/-) 3-(2-Methylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride

The title compound (0.145g) was prepared from amine D3 (0.20g) and 2-methylcinnamic acid (0.16g) according to the method of Example 1
MS $^{m}/_{z}$ (API): 333 (MH^+)

Example 12
(+/-) 3-(2-Nitrophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride
The title compound (0.17g) was prepared from amine D3 (0.20g) and 2-nitrocinnamic acid (0.193g) according to the method of Example 1
MS $^{m}/_{z}$ (API): 364 (MH^+)

Example 13
(+/-) 3-(2-Trifluoromethylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride
The title compound (0.15g) was prepared from amine D3 (0.20g) and 2-trifluoromethylcinnamic acid (0.216g) according to the method of Example 1
MS $^{m}/_{z}$ (API): 387 (MH^+)

Example 14
(+/-) 3-(3-Trifluoromethylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride
The title compound (0.17g) was prepared from amine D3 (0.20g) and 3-trifluoromethylcinnamic acid (0.216g) according to the method of Example 1
MS $^{m}/_{z}$ (API): 387 (MH^+)

Example 15
(+/-) 3-(4-Chloro-2-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride
The title compound (0.17g) was prepared from amine D3 (0.20g) and 4-chloro-2-fluorocinnamic acid (0.20g) according to the method of Example 1
MS $^{m}/_{z}$ (API): 371, 373 (MH^+)

Example 16
(+/-) 3-(2-Chloro-6-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide hydrochloride
The title compound (0.15g) was prepared from amine D3 (0.20g) and 2-chloro-6-fluorocinnamic acid (0.20g) according to the method of Example 1

MS $^{m}/_{z}$ (API): 371, 373 (MH^+)

Example 17

3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)-N-(3-methylphenyl)acrylamide hydrochloride

The acid D22 (0.12g) was converted to the acid chloride by treatment with oxalyl chloride (4ml) in dichloromethane (10ml) containing dimethylformamide (2 drop). The mixture was stirred for 2h at room temperature and solvent removed. The residue was dissolved in tetrahydrofuran (10ml) containing triethylamine (0.5mL) and 3-methylaninline 100uL) added. The mixture was stirred for 16h. solvent removed at reduced pressure, the residue dissolved in dichloromethane (10ml) and washed with water. The organic phase was dried (MgSO4), and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 10%NH3/MeOH in dichloromethane 5:95) to give the title compound (0.069g) after conversion to the hydrochloride salt.

^{1}H NMR - (250MHz, CDCl3 free base) δ 1.66 – 1.99 (3H, m), 2.33 – 2.69 (3H, m), 2.35 (3H, s), 2.81 – 2.89 (1H, m), 3.04 – 3.25 (3H, m), 3.40 (1H, m), 6.50 (1H, d, J = 15.5Hz), 6.94 (1H, d, J = 7.2Hz), 7.12 – 7.39 (6H, m), 7.47 (1H, br. s.) and 7.69 (1H, d, J = 15.4Hz).

MS $^{m}/_{z}$ (API): 333 (MH^+)

PHARMACOGICAL DATA

1. Binding Assay Method

WO 92/22293 (SmithKline Beecham) discloses compounds having anti-convulsant activity, including *inter alia* the compound *trans*-(+)-6-acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (hereinafter referred to as Compound A). It has been found that the compounds of WO 92/22293 bind to a novel receptor obtainable from rat forebrain tissue, as described in WO 96/18650 (SmithKline Beecham). The affinity of test compounds to the novel receptor site is assessed as follows.

Method

Whole forebrain tissue is obtained from rats. The tissue is first homogenised in buffer (usually 50mM Tris/HCl, pH 7.4). The homogenised tissue is washed by centrifugation and resuspension in the same buffer, then stored at -70°C until used.

To carry out the radioligand binding assay, aliquots of tissue prepared as above (usually at a concentration of 1-2mg protein/ml) are mixed with aliquots of [3H]-Compound A dissolved in buffer. The final concentration of [3H]-

Compound A in the mixture is usually 20nM. The mixture is incubated at room temperature for 1 hour. [3H]-Compound A bound to the tissue is then separated from unbound [3H]-Compound A by filtration through Whatman GF/B glass fibre filters. The filters are then washed rapidly with ice-cold buffer. The amount of radioactivity bound to the tissue trapped on the filters is measured by addition of liquid scintillation cocktail to the filters followed by counting in a liquid scintillation counter.

In order to determine the amount of "specific" binding of [3H]-Compound A, parallel assays are carried out as above in which [3H]-Compound A and tissue are incubated together in the presence of unlabelled Compound A (usually 3 μM). The amount of binding of [3H]-Compound A remaining in the presence of this unlabelled compound is defined as "non-specific" binding. This amount is subtracted from the total amount of [3H]-Compound A binding (i.e. that present in the absence of unlabelled compound) to obtain the amount of "specific" binding of [3H]-Compound A to the novel site.

The affinity of the binding of test compounds to the novel site can be estimated by incubating together [3H]-Compound A and tissue in the presence of a range of concentrations of the compound to be tested. The decrease in the level of specific [3H]-Compound A binding as a result of competition by increasing concentrations of the compound under test is plotted graphically, and non-linear regression analysis of the resultant curve is used to provide an estimate of compound affinity in terms of pKi value.

Results

Compounds of this invention were active in this test with pKi values greater than 6. For example, the compound of Example 1 gave a pKi value of 8.6.

2. MEST Test

The maximal electroshock seizure (MEST) threshold test in rodents is particularly sensitive for detecting potential anticonvulsant properties[1]. In this model, anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

Method for mouse model

Mice (naive male, Charles River, U.K. CD-1 strain, 25 - 30g) are randomly assigned to groups of 10 - 20 and dosed orally or intraperitoneally at a dose volume of 10 ml/kg with various doses of compound (0.3 - 300 mg/kg) or vehicle. Mice are then subjected at 30 or 60 min post dose to a single electroshock (0.1 sec, 50Hz, sine wave form) administered via corneal electrodes. The mean current and

standard error required to induce a tonic seizure in 50% (CC_{50}) of the mice in a particular treatment group is determined by the 'up and down' method of Dixon and Mood (1948)[2]. Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)[3].

In control animals the CC_{50} is usually 14 - 18 mA. Hence the first animal in the control group is subjected to a current of 16 mA. If a tonic seizure does not ensue, the current is increased for a subsequent mouse. If a tonic convulsion does occur, then the current is decreased, and so on until all the animals in the group have been tested.

Studies are carried out using a Hugo Sachs Electronik Constant Current Shock Generator with totally variable control of shock level from 0 to 300 mA and steps of 2 mA are usually used.

Method for rat model

The threshold for maximal (tonic hindlimb extension) electroshock seizures in male rats (Sprague Dawley, 80 - 150g, 6 weeks old) was determined by a Hugo Sachs Electronik stimulator which delivered a constant current (0.3 sec duration; from 1-300mA in steps of 5-20mA). . The procedure is similar to that outlined above for mouse and full details are as published by Upton et al,.[4]

The percentage increase or decrease in CC_{50} for each group compared to the control is calculated.

Drugs are suspended in 1% methyl cellulose.

References

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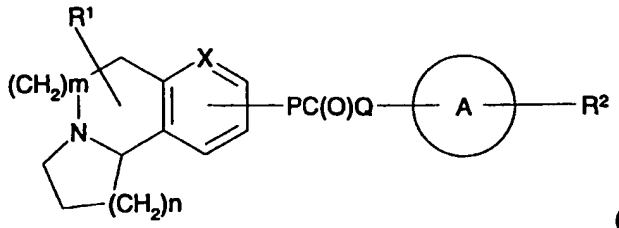
2. Dixon, W.J. and Mood, A.M. (1948). J. Amer. Stat. Assn., **43**, 109-126
3. Litchfield, J.T. and Wilcoxon, F.(1949). J. Pharmacol. exp. Ther., **96**, 99-113
4. N.Upton, T.P.Blackburn, C.A.Campbell, D.Cooper, M.L.Evans, H.J.Herdon, P.D.King, A.M.Ray, T.O.Stean, W.N.Chan, J.M.Evans and M.Thompson. (1997). B. J. Pharmacol., **121**, 1679-1686

Results for rat MEST

Compounds of this invention dosed by the oral route as a suspension in methyl cellulose and tested one hour post dosing show an increase in seizure threshold. For example, at a dose of 2 mg/kg p.o. the compound of Example 1 showed a statistically significant increase of 432.

Claims

1. A compound of formula (I) or a salt thereof or a solvate thereof



(I)

in which:

X is CH or N;

P is -CH=CH- and Q is -NR^6-, or;

P is -CH=CH- and Q is –NR^6CH2-, or;

P is –NH- and Q is –CR^3=CH-;

R^6 is hydrogen, phenylC_{1-6}alkyl, or C_{1-6}alkyl;

R^3 is hydrogen, halo, phenylC_{1-6}alkyl, or C_{1-6}alkyl;

A is a monocyclic aromatic carbocyclic or heterocyclic compound or a bicyclic carbocyclic or heterocyclic compound in which one ring is aromatic;

m is 1 or 2;

n is 1 or 2;

R^1 is hydrogen or up to two substituents selected from fluoro or C_{1-6} alkyl;

R^2 is hydrogen or up to four substituents selected from halogen, NO_2, CN, N_3, CF_3O-, CF_3S-, CF_3CO-, trifluoromethyldiazirinyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}perfluoroalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkylO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, C_{1-6}alkylS-, C_{1-6}alkylSO_2-, $(C_{1-4}alkyl)_2NSO_2$-, $(C_{1-4}alkyl)NHSO_2$-, $(C_{1-4}alkyl)_2NCO$- , oxazolyl, $(C_{1-4}alkyl)NHCO$- or $CONH_2$;

or -NR^4R^5 or -$NHCOR^4$ where R^4 is hydrogen or C_{1-4} alkyl, and;

R^5 is hydrogen, C_{1-4}alkyl, formyl, -CO_2C_{1-4}alkyl or -COC_{1-4}alkyl;

or two R^2 groups are linked together form a carbocyclic or heterocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O;

R^3 ishydrogen, halogen, phenylC_{1-6} alkyl, or C_{1-6} alkyl;

or R^3 and an R^2 are linked together form a saturated or unsaturated carbocyclic or heterocyclic ring.

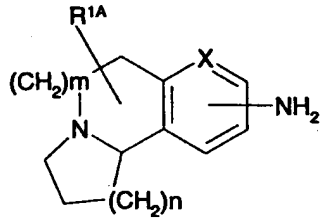
2. A compound of formula (I) according to claiom 1 having
R^1 as hydrogen, fluoro, methyl, ethyl or propyl;
R^2 as hydrogen or one or more of methyl, ethyl, *n*-butyl, phenyl, *iso*-propyl, *t*-butyl, methoxy, ethoxy, n-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amino, acetylamino, methylthio, oxazolo, methylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl;
R^3 as hydrogen, fluoro, methyl, ethyl or propyl.
Suitable linked R^2 groups include -CH=CH-NH-.

3. A compound of formula (I) according to claim 1or claim 2 wherein
R^1 is hydrogen,
R^2 is hydrogen or one or more of ethyl, methoxy, trifluoromethyl, cyano, chloro, fluoro.

4. A compound according to any one of claims 1 to 3 selected from:
3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Methoxyphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Chlorophenyl)-N-(6,6-dimethyl-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Chloro-6-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Acetylaminophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Acetylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Cyanophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)-3-[2-(2-oxopyrrolidin-1-yl)phenyl]acrylamide;

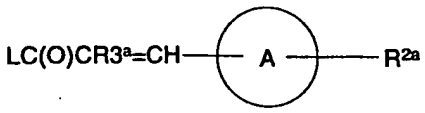
3-(2-Chlorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Methylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Nitrophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Trifluoromethylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(3-Trifluoromethylphenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(4-Chloro-2-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide;
3-(2-Chloro-6-fluorophenyl)-N-(1,2,3,5,6,10b-hexahydropyrrolo-[2,1-a]isoquinolin-9-yl)acrylamide, and;
3-(1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-9-yl)-N-(3-methylphenyl)acrylamide.

5. A process for the preparation of compounds of formula (I) as defined in claim 1, or a salt thereof or a solvate thereof, wherein P is –NH- and Q is –CR^3=CH-, which comprises reacting a compound of formula (II)



(II)

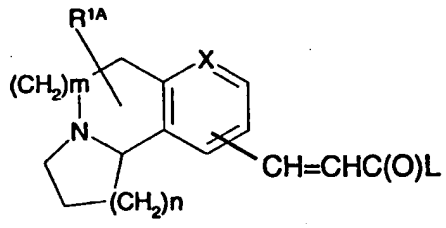
where m and n are as defined for formula (I), R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1;
with a compound of formula (III)



(III)

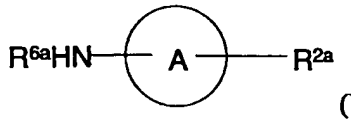
where R^{2a} and R^{3a} are independently R^2 or R^3 as defined for formula (I) or a group or groups convertible to R^2 or R^3; A is as defined for formula (I), and L is OH, acyloxy, or a halogen;
and where required,
converting an R^{1A}, R^{2a} or R^{3a} group to an R^1, R^2 or R^3 group;
converting one R^1, R^2 or R^3 group to another R^1, R^2 or R^3 group;
converting a salt product to the free base or another pharmaceutically acceptable salt, or;
converting a free base product to a pharmaceutically acceptable salt.

6. A process for the preparation of compounds of formula (I) as defined in claim 1 or a salt thereof or a solvate thereof wherein P is –CH=CH- and Q is —NR^6-, or where P is –CH=CH- and Q is —CH_2NR^6-which comprises reacting a compound of formula (IV)

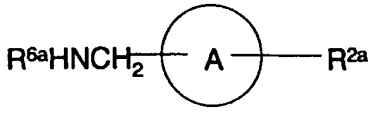


(IV)

where m and n are as defined for formula (I), R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1;
with a compound of formula (V) or (VI)



(V)



(VI)

where R^{2a} and R^{6a} are independently R^2 or R^6 as defined for formula (I) or a group or groups convertible to R^2 or R^6; A is as defined for formula (I), and L is OH, acyloxy, or a halogen;
and where required,

converting an R^{1A}, R^{2a} or R^{6a} group to an R^1, R^2 or R^6 group;
converting one R^1, R^2 or R^6 group to another R^1, R^2 or R^6 group;
converting a salt product to the free base or another pharmaceutically acceptable salt, or;
converting a free base product to a pharmaceutically acceptable salt.

7. A pharmaceutical composition for use in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), which comprises a compound of formula (I) as defined in claim 1; or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

8. A method of treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity

(spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof.

9. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

10. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes,

multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/EP 99/05586

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/435 //(C07D471/04,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HU 154 952 B (GYOGYSZERKUTATO INTEZET) 25 July 1968 (1968-07-25) claims 1-5	1-10
A	GB 2 160 862 A (JOHN WYETH & BROTHER LIMITED) 2 January 1986 (1986-01-02) claims 1-12	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
22 November 1999	30/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Herz, C

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/05586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
HU 154952 B		NONE	
GB 2160862 A	02-01-1986	US 4604398 A	05-08-1986